Main Submission

It's In Your Genes: Recent Considerations in Germline versus Somatic Gene Therapy

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Introduction

Although the notion of a "designer baby" seems to be dAs of February 14th 2017, the National Academy of Sciences endorsed the use of germline therapy in certain well-defined cases, resulting in immediate responses of public controversy and discussion (1). In its public release, the National Academy of Sciences compounded the findings of 22 scientists over the past year, consolidating the research of leading experts in both science policy and genetics. While this was not a change in legislation, and in fact opposes pro-life legislation prohibiting FDA approval of genetically modifying embryos, the released guidelines were a significant step towards making germline gene therapy more available (1). Ultimately, this may lead to policy reform in North America and Europe for both somatic and germline gene therapies.

Both somatic and germline gene therapies involve therapeutic delivery of nucleic acids into a patient's cells, in order to induce functional changes into the genetic code (Figure 1) (2). The process of somatic gene therapy only affects individual body cells and cannot be passed to offspring (3). In contrast, germline gene transfer involves genetic modification of tissues that are inherited from one generation to the next. As such, the germline technology carries certain ethical issues beyond those of somatic gene therapy. Somatic therapy has often been favoured by legislators due to its minimal risks and relative transiency. Over 600 clinical trials involving somatic gene therapy are currently running in the United States, targeting immunodeficiencies, cystic fibrosis, and clotting pathologies (4). However, germline therapy continues to be prohibited in Canada, the United States, and most of western Europe, due to the ethical issues associated with manipulating future generations, and the unknown consequences that may arise (4).

Current Challenges

There are several risks associated with germline gene therapy, particularly as research in germline therapy has been stagnant due to restrictions in funding; these restrictions prevent further information on the

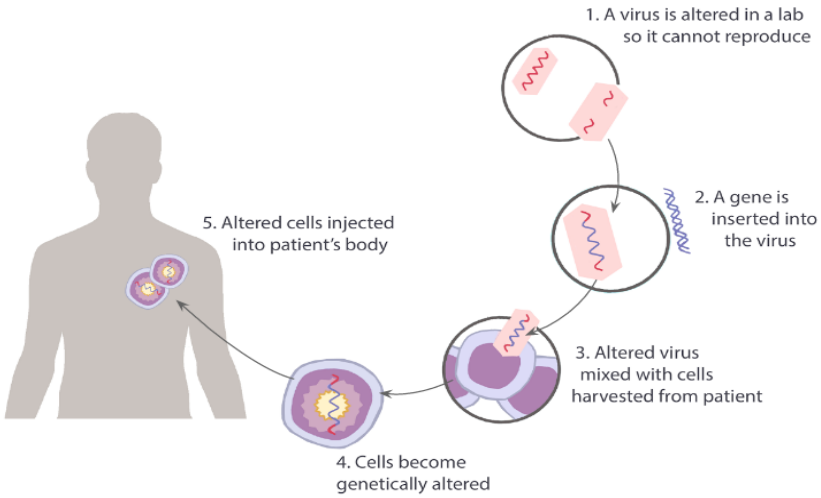

Figure 1: Simple model of the gene therapy process.

future consequences of germline gene therapy from being explored. Foremost, germline gene therapy has demonstrated the difficulty in transferring genetic vectors into spermatocytes or oocytes (5). While these complications can be easily detected in animal models, this may prove to be logistically difficult in human embryos. Multiple or partial gene copies could not only prove to be embryonic lethal, but could also remain dormant and be passed onto future generations to magnify any possible complications (5). This poses particular risk for polygenic diseases, which do not fit simple Mendelian disease models. In addition, germline gene therapy could pose risks as a platform for eugenics (6), or could be used to select physical characteristics that are unrelated to health. With steps being taken to make germline gene therapy more available, the response from the public has predominantly focused on the ever-present risk of "designer babies." While the National Science Agency panel explicitly stated that this technology not be legislated unless its sole purpose was health-related, the classification of "health-related reasons" is often contested (1,6). For example, there is a current stakeholder controversy regarding the use of genetic technology regarding disability (7). As such, any potential applications of germline gene therapy would require extensive regulation and appraisal.

Potential Advantages

Nonetheless, germline gene therapy remains highly promising due to its clinical applications. Not only can germline gene therapy treat single-gene diseases in individual patients, it also has the potential to completely remove a disease from the population (5,8). This would not only ensure public health in a manner similar to vaccines and population-based interventions, but also reduce the long-term health costs related to treating the disease. Over 24 million people in the United States alone are affected by autoimmune diseases with a heritable component, with treatment options often characterized by symptom management rather than providing an outright cure (9).

Conclusions

The recent developments from the National Academy of Sciences may inspire international reform regarding the genetic editing of gametes. As the United States government does not currently support federal funding for germline gene therapy, it is important for the research field to gain further awareness (5). The regulatory suggestions from the National Academy of Science are a significant step in allowing narrow, well-defined subsets of germline applications to be investigated for clinical potential. However, future steps, such as financial and political support from major North American government parties, are necessary for progress in gene therapy. ■

References

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Table 1: Disorder prevalence for single-gene disorders in live infant births in the United States.

Autosomal dominant	
Huntington's disease	1 in 15,000
Hereditary spherocytosis	1 in 5,000
Marfan syndrome	1 in 4,000
Neurofibromatosis type I	1 in 2,500
Autosomal recessive	
Galactosemia	1 in 57,000
Lysosomal acid lipase deficiency	1 in 40,000
Mucopolysaccharidoses	1 in 25,000
Phenylketonuria	1 in 12,000
X-linked	
Hemophilia	1 in 10,000
Duchenne muscular dystrophy	1 in 7,000

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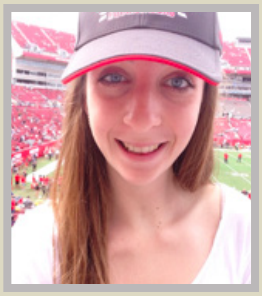

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